REMARKS

Applicants have received and reviewed an Office Action dated August 13, 2002. By way of response, Applicants have amended claim 11. The amendmnet to claim 11 is supported throughout the specification including at page 9 line 31 to page 10 line 2; page 16, lines 22-33; and page 19 lines 23-29. No new matter is presented. Claims 11, 31-32, and 34 are pending. Applicants submit that the pending claims are supported by the specification.

Priority

The specification has been amended to more clearly reflect, on page 1, the relationship of PCT application No. PCT/US00/13975 with the present application. The Examiner has requested a certified copy of PCT/US00/13975 but the Applicants understand 35 U.S.C. § 119(b) does not require a certified copy when the PCT is filed with the USPTO receiving office. If the Applicants misunderstand and the Examiner maintains that a certified copy is required, one will be submitted.

Information Disclosure Statement

Applicants note that an IDS and 13 references were filed with the preliminary amendment dated November 26,2001. Applicants have not received the initialed 1449 form. Applicants request that the Examiner consider the references and return the initialed 1449 form to Applicants.

Petition for Extension of Time

It is noted that a three-month petition for extension of time is necessary to provide for the timeliness of the response. A request for such an extension is made extending the time for response from November 13, 2002 to February 13, 2003.

Embedded Hyperlink

The specification has been amended to remove the embedded hyperlink. Applicants respectfully request withdrawal of the objection to the specification.

35 U.S.C. 132 – New Matter

The Examiner objected to the preliminary amendment filed on June 19, 2002 as introducing new matter into the disclosure. Specifically, the Examiner asserts that substituting SEQ ID NO:43 with SEQ ID NO:42 on page 26-27 is not supported by the specification and the claims as originally filed. Applicant respectfully traverses this objection on the basis that this preliminary amendment simply rectified an obvious error and did not introduce any new matter.

The Examiner asserted that Table 3 supports the view that new matter is being added by amending the sequence ID NO. The Examiner articulates this contention stating that, "[i]t is noted that Table 3 shows SEQ ID NO: 42 to be expressed in Gastrointestinal tissue but not islet cells and islet cell tumor."

On the contrary, the information contained in Table 3 supports the fact that substituting SEQ ID NO: 43 with SEQ ID NO: 42 is merely the correction of an obvious mistake. Table 3 shows that SEQ ID NO: 43 is expressed in: 1) reproductive tissue, 2) hematopoietic/immune tissue, and 3) nervous tissue. The specification as originally written states, beginning at page 26, line 33 that "SEQ ID NO:43 is specifically expressed in islet cells and in islet cell tumor only." Since islet cells are not: 1) reproductive tissue, 2) hematopoietic/immune tissue, or 3) nervous tissue it is obvious that what is disclosed at page 26, line 33 and what is disclosed in Table 3 are in conflict and thus, there was a mistake.

The correction of this mistake by substituting SEQ ID NO: 43 with SEQ ID NO: 42 is supported by the teachings of Table 3, contrary to the views of the Examiner. As pointed out by the Examiner, Table 3 shows that SEQ ID NO: 42 is expressed in gastrointestinal tissue. An Islet cell tumor is a tumor of the pancreas. As such, islet cells properly fit under the general classification of gastrointestinal tissue. Thus, in view of Table 3 it is obvious that a clerical error was made in the typing of "SEQ ID NO:43" instead of "SEQ ID NO:42" and that "SEQ ID NO:42 is specifically expressed in islet cells and in islet cell tumor only" because that statement is in accord with Table 3.

In addition, the information in Tables 1 and 2 also support correction of the mistake as an obvious error. Table 1 shows that SEQ ID NO:42 encodes polypeptide SEQ ID NO:16. Table 2 indicates that SEQ ID NO:16 has homology to pancreatic precursor polypeptide. The fact that

SEQ ID NO:42 encodes a polypeptide with homology to a pancreatic precursor polypeptide is consistent with expression in pancreatic tissue. In contrast , in Table 1, SEQ ID NO:43 encodes SEQ ID NO:17. In Table 2, SEQ ID NO:17 has homolgy to fibrosin, which is a cytokine and is consistent with expression in 1) reproductive tissue, 2) hematopoietic/immune tissue, or 3) nervous tissue. Thus, in view of Tables 1 and 2, it is obvious that a clerical error was made in the typing of the SEQ IDs and that "SEQ ID NO:42 is specifically expressed in islet cells and in islet cell tumor only" because that statement is also in accord with the information presented in Tables 1 and 2.

The change in the SEQ ID number on page 26 was clearly the correction of an obvious mistake and the true SEQ ID numbers are provided by the data in Tables 1, 2 and 3. Applicant asserts no new matter was introduced. By the amendment, for at least these reasons, Applicant respectfully requests that the objection to the preliminary amendment filed on June 19, 2002 be withdrawn and the amendment be entered.

35 U.S.C. 112 - Indefiniteness

The Examiner rejected claims 34 and 36-41 under 35 U.S.C. §112, second paragraph, as indefinite. Applicants respectfully traverse this rejection.

Claim 34

Specifically, the Examiner asserts that "claim 34 has no antecedent basis in base claim 32, because claim 32 recites a composition comprising an antibody per se, whereas a labeled antibody is recited in claim 34." Applicant traverses this rejection.

MPEP §2173.05(e) provides that a lack of antecedent basis may arise where it is unclear as to what element a given limitation references. Claim 32 recites "a composition comprising an antibody of claim 11 and an acceptable excipient." Claim 34 recites "a composition of claim 32, wherein the antibody is labeled." Thus, in Claim 34, Applicant has put a limitation on one of the elements of the composition, specifically that the antibody is labeled. It cannot reasonably be suggested that it is unclear as to which of the elements in the composition the limitation of claim 34 refers. Therefore, there is no lack of antecedent basis according to MPEP §2173.05(e).

Claims 36 and 39

The Examiner asserts that "the term 'specificity' recited in claim 36, line 1 and claim 39, line 1 is ambiguous and unclear and the metes and bounds of the claimed 'specificity' is not defined." Applicant traverses this rejection.

MPEP §2173.05(b) provides that "acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." The Examiner's attention is drawn to the paragraph beginning at page 23, line 27 of the application where the Applicants have provided a definition for the term "specificity." Here, the Applicants state that "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The Applicants further state that the interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. Beyond the definition provided by the Applicants, the term "specificity" is widely used and understood in the art of antibody technology. For example, in a basic text on Immunology, Kuby defines specificity as the capacity of antibody and T-cell receptor to recognize and interact with a single, unique antigenic determinant. See Kuby, 1994, *Immunology*, 613. As such, one of skill in the art readily understands what is meant by the term "specificity."

For at least these reasons, Applicants respectfully request that the indefiniteness rejections be withdrawn.

35 U.S.C. 101 - Utility

The Examiner rejected claims 11, 31, 32, 34 and 36-43 under 35 U.S.C. §101 as not supported by either a specific and/or substantial asserted utility or a well established utility. The Examiner asserts that the instant specification does not disclose a biological role for the claimed peptide or a credible "real world" use for the claimed antibodies and therefore does not meet the requirements of 35 U.S.C. §101 as being useful. Applicant respectfully traverses this argument.

The Examiner's argument hinges on the assertion that the utilities disclosed are not specific and substantial because the specification fails to disclose any particular function or biological significance for EXCS. The Examiner asserts that although the disclosed polypeptide

is said to have amino acid sequence similarity to other known proteins, that it would require further research to find specific and substantial credible utility for the claimed isolated compositions. According to the Utility Guidelines referred to by the Examiner, specific utility is that which is specific to the subject matter claimed. Thus, specific utility requires something more than a statement of diagnosing an unspecified disease, such as, a disclosure of what condition can be diagnosed. The Utility Guidelines further state that substantial utility defines a "real world" use. Further, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. The invention as presently claimed clearly has both specific and substantial utility according to these guidelines.

First, the invention as claimed has specific utility because it has been disclosed that antibodies to SEQ ID NO: 16 can be used to diagnose islet cell tumors. Second, the invention as claimed has substantial "real world" utility as it is demonstrated that SEQ ID NO: 16 has homology to pancreatic polypeptide and it is well known that the presence of pancreatic polypeptide is a marker for islet cell tumors. The Examiner's attention is drawn to Table 2 where the Applicant discloses that polypeptide SEQ ID NO: 16 shows significant homology to pancreatic polypeptide precursor (gp190270), including signature sequence for the signal, pancreatic hormone peptide, and precursor motifs. It is known that high circulating levels of pancreatic polypeptide are diagnostic of certain tumors of the pancreas. See Adrian et al., 1986, *N. Engl. J. Med.*, 315:287-291; Bordi et al., 2002, *Peptides*, 23(2):339. Finally, diagnostic tests available in the commercial market irrefutably demonstrate that antibodies that bind pancreatic polypeptide have "real world" credible use. For example, IBL Immuno-Biological Laboratories sells a radio-immuno assay kit to test serum levels of pancreatic polypeptide because "elevated fasting levels of pancreatic polypeptide in serum are found at the occurrence of pancreatic polypeptide producing tumors and endocrine tumors in the pancreas and in the gastrointestinal tract." See IBL Immuno-Biological Laboratories, Cat. No. MI-1131 (copy attached). Because of the demonstrated homology between SEQ ID NO: 16 and pancreatic polypeptide, as well as the demonstrated selective production of SEQ ID NO: 16 in islet cells and islet tumors, a specific, substantial, and credible utility for anti-SEQ ID NO: 16 antibodies is provided by the specification.

The Examiner cites Leiter et al., 1985, *J. Biol. Chem.*, 260:13013-13017 for the proposition that the gene detected in a pancreatic polypeptide-producing islet cell tumor was indistinguishable from that in normal human leukocytes. Leiter states that Southern blots of genomic DNA isolated from a pancreatic polypeptide-producing tumor were indistinguishable from those obtained using normal human leukocyte DNA. See id. at 13016. The Examiner uses this reference to assert pancreatic-polypeptide can be expressed in non-islet cells. Although both normal and tumor islet cells express pancreatic polypeptide, this does not take away from the utility of the invention as claimed. Antibodies to SEQ ID NO: 16 have utility as a marker of many pancreatic endocrine tumors. See Adrian et al., cited supra. Adrian discusses plasma concentration of pancreatic polypeptide as a marker for pancreatic endocrine tumors. Moreover, Adrian discusses methods, such as atropine suppression, by which tumor-related secretion of pancreatic polypeptide can be distinguished from normal secretion of pancreatic polypeptide. As such, the expression of pancreatic polypeptide by normal islet cells does not negate the utility of antibodies to SEQ ID NO: 16.

The Examiner cites Attwood (*Science* 2000; 290:471-473) for the proposition that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." However, Applicants point out that homology to sequences of known function is a commonly used and reliable technique in the art for elucidating function. *See* Bonneau et al., 2001, *J. Struc. Biol.*, 134:186 at 187; Brenner et al, 1998, *Proc. Natl. Acad. Sci.*, 95:6073-6078. Even "*ab initio* structure prediction ... is well suited to help interpret the function of the significant fraction of genes in sequenced genomes that do not have detectable sequence similarity to proteins of known structure or function." Bonneau et al., cited supra. In light of that, functional determinations where there is sequence homology to known structures and where known motifs have been identified is not presumptuous. The Examiner's attention is drawn to Table 2 where it is disclosed that motifs for pancreatic hormone peptide and pancreatic hormone precursor are identified in Polypeptide SEQ ID NO: 16.

For at least these reasons, Applicants respectfully request that the utility rejections be withdrawn.

35 U.S.C. 112 – Enablement

The Examiner rejected claims 11, 31, 32, 34 and 36-43 under 35 U.S.C. §112, first paragraph, as not enabled by the specification. Specifically, the Examiner states that there is insufficient guidance and direction as to how to make the claimed antibodies. Applicant respectfully traverses this argument.

Examiner's attention is drawn to example XIII beginning at page 62, line 31. In this example, Applicants provide sufficient disclosure to enable the production of specific antibodies raised against specific antigens. Based on this disclosure and the fact that the production of antibodies against a characterized antigen is a mature technology where the level of skill is high and advanced, Applicants assert one of skill in the art is enabled to make antibodies as claimed.

Further, the Examiner attempts to show unpredictability in the field by citing references where single amino acid changes in an antigen abolish antibody binding. The instant claims are directed to antibodies that bind specific antigens. As stated above, one of skill in this area is fully enabled to produce an antibody that recognizes the specific antigens listed in the claims.

For at least these reasons, Applicants respectfully request that the utility rejections be withdrawn.

35 U.S.C. 112 – Written Description

Claims 11, 31, 32, 34 and 36-43 are rejected under 35 U.S.C. §112, first paragraph, lacking written description. Specifically, the Examiner acknowledges sufficient written description is provided for an antibody that binds the peptide of SEQ ID NO: 16, but asserts adequate description is not provided for antibodies that bind the scope of peptides listed in the claims.

Example 16 of the USPTO Written Description Guidelines referenced by the Examiner provides that it is well known that antibodies can be made against virtually any protein. Further, this example provides that antibody production is a mature technology where the level of skill is high and advanced. Representative description of the structural and functional properties of the claimed antibodies has occurred. Applicants have provided sequence data for the peptide antigen and structural information relating thereto. Exemplary is the disclosure of SEQ ID NO: 16 with the identification of known motifs in the sequence. Further, as discussed previously, homology

information is disclosed which provides a reasonable basis by which to determine function. Therefore, according to the Written Description Guidelines, Applicants assert that one of skill in the art would have recognized that the spectrum of antibodies that bind to SEQ ID NO: 16, or a polypeptide having at least 90% identity thereto, were disclosed as a result of the isolation of SEQ ID NO: 16. Therefore, Applicants assert that the specification is adequate to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed antibodies and request that this rejection be withdrawn.

SUMMARY

Applicants submit the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted.

Respectfully submitted,

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MARKED-UP VERSION TO SHOW CHANGES MADE

IN THE SPECIFICATION

The paragraph beginning at page 1, line 3, has been amended as follows:

--This application is a continuation [claims the benefit] of Patent Cooperation Treaty International application Ser. No. PCT/US00/13975, filed May 19, 2000, entitled EXTRACELLULAR SIGNALING MOLECULES, which claims the benefit of U.S. Provisional applications U.S. Ser. No. 60/134,949, filed May 19, 1999, U.S. Ser. No. 60/144,270, filed July 15, 1999, U.S. Ser. No. 60/146,700, filed July 30, 1999, and U.S. Ser. No. 60/157,508, filed October 4, 1999. All of these applications are hereby expressly incorporated by reference herein.--

The paragraph beginning at page 56, line 29, has been amended as follows:

--The genetic map location of SEQ ID NO:47 is described in The Invention as a range, or interval, of a human chromosome. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "Genemap'99" World Wide Web site [(http://www.ncbi.nlm.nih.gov/genemap/)] (ncbi.nlm.nih.gov at /genemap/) can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.--

IN THE CLAIMS

11. (Amended) An isolated antibody [which] that specifically binds to a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:16;

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:16; and

c) a biologically active fragment of a polypeptide, the fragment having at least 90% identity with the amino acid sequence of SEQ ID NO:16.[; and

[d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO :16.]